CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ETHYLENE DIBROMIDE

SB 950-168, Tolerance #126

October 22, 1986

I. DATA GAP STATUS

Chronic rat: Data gap, no studies on file

Chronic dog: Data gap, no studies on file

Onco rat: No data gap, possible adverse effect

Onco mouse: No data gap, possible adverse effect

Repro rat: Data gap, no studies on file

Terato rat: Data gap, inadequate study on file, possible adverse effect indicated

Terato mouse: Data gap, inadequate study on file, insufficient data to assess for adverse effect

Gene mutation: No data gap, possible adverse effects

Chromosome: No data gap, possible adverse effects

DNA damage: No data gap, possible adverse effects

Neurotox: Not required

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name 10b SB168ETH.JAP
Index VdV 10/20/86. Reviewed JCC 10-21-86 and JG, 10/22/86

II. TOXICOLOGY ONE-LINERS AND DISCUSSION

CHRONIC

RAT

No study on file.

DOG

No study on file.

ONCOGENICITY

RAT

001 27257 (Hazleton, 7/30/73). J. Natl. Cancer Inst. 51, 1993-1995. AA, 5/13/85. Ethylene dibromide (96%) given by oral gavage at 40 and 80 mg/kg for 54 weeks; at week 16 high dose discontinued for 14 weeks, at week 30 high dose group converted to 40 mg/kg; 20/sex/control (vehicle and untreated) group; 50/sex/treatment group; high mortality in both sexes at high dose level and in females at low dose level; data for week 54 show increased incidence of squamous cell carcinomas of stomach at both dose levels; no NOEL established; UNACCEPTABLE (only two dose levels, inadequate controls, no individual data, high mortality, changing of dosing levels and period of no dosing during the study), NOT UPGRADEABLE.
Note: A more complete version of this study is identified as record # 27253 in volume 015. Inconsistencies noted in the duration of the study between the NCI report and the publication.

015 27253 (Hazleton for NCI, 1978). NCI Technical Report #86, 1978. AA, 5/13/85. Ethylene dibromide (96-99%) given by oral gavage at 0, 40, or 80 mg/kg for 49 (males) to 61 (females) weeks; after 16 weeks at high dose treatment of males discontinued for 13 weeks followed by 18 weeks at a dosage level of 40 mg/kg with two weeks of no treatment during the last six weeks, low dose males were dosed throughout except for two weeks during the last six; dosing of females in the high dose group similar to the males except that there were 4 weeks of no treatment during the last 16; 50/sex/treatment group, 20/sex/vehicle and no treatment control group; squamous-cell carcinomas of stomach at both dose levels, increased frequency of hemangiosarcomas in the low, but not high, dose group males, increased incidence of hepatocellular carcinomas in females at high dose level; no NOEL established; UNACCEPTABLE (only two dose levels; inconsistent dosing regime; sacrifice of untreated controls at 107 weeks, vehicle controls at 63 weeks, experimental male groups at 49 weeks and experimental female groups at 61 weeks), NOT UPGRADEABLE.

011 27250 (Hazleton for NTP, 1982). NTP Technical Report #210, 1982. AA, 5/13/85. Ethylene dibromide (>99%) by inhalation at 0, 10 and 40 ppm for 6 hrs./day, 5 days/week for 88-103 weeks; high dose males terminated at 89 weeks, high dose females terminated at 91 weeks; 50/sex/group; test article dose-related decreased survival in both sexes, increased incidence of carcinomas and adenocarcinomas of nasal cavity in both sexes at high dose
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level, increased frequency of nasal adenomas and adenocarcinomas in both sexes at low dose level, increased incidence of hemangiosarcomas of circulatory

system and mesotheliomas of the tunica vaginalis in males at high dosage, increased frequency of combined alveolar/bronchiolar adenomas and carcinomas in females at high dose level, at both dose levels an increased incidence of mammary gland fibroadneomas; hepatic necrosis and toxic nephropathy in both sexes, retinal degeneration in female rats, testicular degeneration in males; no NOEL established; UNACCEPTABLE (only two dose levels, no individual data, animals examined for tumor only), NOT UPGRADEABLE.

016 934137 (Wong et al. under NIOSH contract--cited in SRI Quantitative Cancer Risk Assessment for Occupational Exposure to Ethylene Dibromide dated 6/82). AA, 5/14/85. Summary only; Ethylene dibromide (purity not indicated) via inhalation at 20 ppm for 7 hrs/day, 5 days/week for 18 months; 47/sex in the control group, 48/sex in the treated group; increased incidence of tumors of the nasal cavity in both sexes, increased frequency of hemangiosarcomas of the spleen (males), adenocarcinomas of mammary gland, focal proliferation of bronchiolar epithelium in both sexes; no NOEL established; UNACCEPTABLE, NOT UPGRADEABLE.

50507-001 11706 (University of Stockholm, 1980). Mutation Research 76, 269-295 (1980). JG, 10/22/86. Review article. Contains citations on oncogenicity studies in rats and mice with positive effects causing squamous cell carcinomas of the stomach in both species following gastric intubation and skin and lung tumors after skin painting. UNACCEPTABLE.

While none of the oncogenicity studies alone is adequate, there are sufficient data to assess toxicity and the chemical will be designated as oncogenic. No further studies are required.

MOUSE

001 27256 (Hazleton, 7/30/73). J. Natl. Cancer Inst. 51, 1993-1995. AA, 5/13/85. Ethylene dibromide (96%) given by oral gavage at 0, 60 and 120 mg/kg; after 13 weeks doses changed to 100 and 200 mg/kg, at week 15 original doses reinstated; total of 42 weeks of observation; 50/sex/treatment group, 20/sex/control (vehicle and untreated) group; 40 of 50 at high dose level died; no increase in frequency in gastric squamous carcinoma or mammary adenocarcinomas at week 42 are reported; NOEL not established; UNACCEPTABLE; (only two dose levels, high mortality at high dose level, no individual data), NOT UPGRADEABLE.
Note: A more complete version of this study is identified as record # 27252 in volume 015. Several inconsistencies between the two reports are evident.

015 27252 (Hazleton for NCI, l978). NCI Technical Report No. 86, 1978. AA, 5/13/85. Ethylene dibromide (>96%) given by oral gavage at 0, 60, and 120 mg/kg; low dose exposed for 10 weeks to 60 mg/kg followed by 2 weeks at 100 mg/kg then 41 weeks at initial level and 25 weeks without dosing; high dose group exposed for 10 weeks at 120 mg/kg followed by 2 weeks at 200 (continued on next page)

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mg/kg then 27 weeks at 120 mg/kg, 14 weeks at 60 mg/kg and 24-25 weeks without dosing; 20/sex/control (vehicle and untreated) group, 50/sex/treatment group; male mice and high dose females terminated at week 78, low dose females at week 90 (53 of treatment and 37 of observation); dose-related decrease in survival for both sexes, increased incidence of stomach squamous-cell carcinomas in both sexes at both of the dose levels, increased frequency of alveolar/bronchiolar adenomas in males at the high dose level, increased incidence of alveolar/bronchiolar adenomas and carcinomas in low dose females;

no NOEL established; UNACCEPTABLE (high mortality, only two dose levels, irregular dosing regime), NOT UPGRADEABLE.

011 27251 (Hazleton for NTP, 1982). NTP Technical report # 210, 1982. AA, 5/13/85. Ethylene dibromide (>99%) by inhalation at 0, 10, and 40 ppm for 6 hrs/day, 5 days/week; 50/sex/group; male mice on study for 78-79 weeks, high-dose female mice on study for 90 weeks, controls and low-dose females on study for 103-106 weeks; dose-dependent decrease in female survival, early and high mortality in all male groups; increased incidence of alveolar/bronchiolar carcinomas and adenomas in both sexes at high dose level, increased frequency of hemangiosarcomas in females at both dose levels, increased subcutaneous fibrosarcomas and nasal cavity carcinomas in high-dosed females, low-dosed females showed increased frequency of mammary gland adenocarcinomas; epithelial hyperplasia in respiratory system; no NOEL established; UNACCEPTABLE (only two dose levels, high mortality, no individual data), NOT UPGRADEABLE.

While neither of the oncogenicity studies alone is adequate, there are sufficient data to assess toxicity and the chemical will be designated as oncogenic. No further studies are required.

REPRODUCTION

001 934133 Journal article (Reprod. Fert. 44, 561-565--1975) dealing with the potential reproductive effects of EDB on bulls (unacceptable species for SB950 study). Effects on spermatogenesis and sperm maturation reported.

TERATOGENICITY

RAT

001 27254 (Midwest Research Institute for EPA, 4/76). AA, 5/10/85. Ethylene dibromide (purity not indicated) by inhalation 23 hrs/day on days 6-15 of gestation at 0 and 32 ppm actual (food-restricted controls also included); 17-18/group; test article associated with fewer fetuses/dam, fourth ventricle hydrocephaly in fetuses; no NOEL established; UNACCEPATBLE (only one dose level, test article not characterized, no individual data, incomplete set of parameters, measured), NOT UPGRADEABLE.

MOUSE

001 27255 (Midwest Research Institute for EPA, 4/76). AA, 5/10/85. Ethylene dibromide (purity not indicated) by inhalation 23 hrs/day on days 6-15 of gestation at 0 and 32 ppm actual (food-restricted controls also included); 9-17/group; tendency towards increased resorptions, decreased fetal weight, third and fourth ventricle hydrocephaly, several skeletal anomalies; effects possibly related to decreased food intake as a similar incidence was found in feed-restricted group; no NOEL established; UNACCEPTABLE (only one dose level, test article not characterized, no individual data, incomplete set of parameters measured, inadequate number of animals/group, incomplete description of methods), insufficient information to evaluate possible teratogenic effect.

Microbial Systems

50507-001 27259 (New York Med. College, 12/77). Environ. Health Perspectives 21, 79-84. AA, 5/13/85. Ethylene dibromide (purity not indicated) tested on Salmonella strains TA1530, TA1535 and TA1537 without S9; dose-dependent increase of TA1530 revertants from 0 to 15 ug EDB/plate, mutation frequency of TA1535, but not TA1537, increased with 10 ug test article/plate; UNACCEPTABLE (methodology not described, inadequate number of dose levels tested, no metabolic activation, test article not characterized, no individual data, inadequate number of strains used), NOT UPGRADEABLE.

50507-001 No record number (Eastman Kodak, 1981). Mutation Research 90, 31-48 (1981). JG, 10/22/86. Ethylene dibromide (99.89%) tested in Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation at 0, 14.1, 28.2, 56.41 or 111.76 umoles per plate. EDB was positive in a concentration dependent manner both with and without activation in TA1535, TA98 and TA100. The report states that none of the 10 halogenated alkane solvents tested were positive in the strains TA1537 and TA1538. The main thrust of the publication is the design of a closed container for testing volatile solvents. Only EDB and 1-bromo-2-chloroethane were positive in the standard plate incorporation procedure indicating that the mutagenic activity of volatile compounds may be missed.
UNACCEPTABLE (no repeat trial, no individual plate counts).

50507-001 No record number (University of Leiden, 1981). Carcinogenesis 2, 499-505 (1981). JG, 10/22/86. Ethylene dibromide (>99.5%) tested in Salmonella strain TA100 with and without rat liver activation with 100,000g

supernatant (S100); concentration dependent increase in reversion rate without activation from 0 to 4 mM; with the addition of S100, an even greater rate of reversion occurred.

Mammalian Systems

**** 50507-001 11705** (Oak Ridge Natl. Lab, 81). Mutation Research 90, 183-191 AA, 5/13/85. Ethylene dibromide (purity not indicated) tested in the CHO/HGPRT system +/- S9 at 0 to 0.5 mM with activation and 0 to 5 mM -S9 for 5 hours; 5 plates per concentration for mutagenicity; 3 mM EDB showed marked cytotoxicity, dose-related increase in mutation frequency with test article; ACCEPTABLE (data presented graphically.)

MISCELLANEOUS

50507-001 11706 (University of Stockholm, 1980). Mutation Research 76, 269-295 (1980). JG, 10/22/86. Review of the literature on ethylene dibromide and ethylene dichloride. Salmonella strains G46, TA1530, TA1535 and TA100 were reverted without metabolizing enzymes. Serratia marcescens (a21 and a742) and E. coli (Gal R^S) are induced for back and forward mutations respectively. Salmonella strain G46 gave positive results both in vitro and in a host-mediated assay in NMRI mice. Other studies with microorganisms also cited. Several reports are cited showing that EDB increases the sex-linked recessive lethals in Drosophila with the spermatids and the spermatocytes being 10-20 times more sensitive than the spermatozoa. EDB is positive both with and without activation for inducing mutations in mouse lymphoma (L5178Y) cells with enhanced activity with S9.

SUMMARY: Data gap is filled by 11705. In addition, there are numerous studies in the published literature that show EDB is mutagenic in a number of test systems including Drosophila. EDB is a direct acting mutagen not requiring activation; in some circumstances, the activity is further enhanced by addition of enzyme activation.

CHROMOSOME

NO COMPLETE STUDIES ON FILE

50507-001 11706 (University of Stockholm, 1980). Mutation Research 76, 269-295 (1980). JG, 10/22/86. Review of publications on EDB. Cites a report on the induction of sister chromatid exchanges in Chinese hamster V79 cells when exposed to 0.5 to 5 mM EDB in a concentration dependent manner. The increase was from 15.2 to 46.9 SCEs/cell compared with 6.1 for control. Chromosomal aberrations were also induced in V79 cells with aberrations in 16 and 71% of the cells at 2 and 5 mM respectively; control was 1.8%. The 5 mM also caused polyploidy in 9.5% of the cells compared with 1.5% in the control. EDB was negative at 50-100 mg/kg in the mouse dominant lethal test. Another report, however, using Wistar rats, showed subfertility in week 3 and infertility in week 4 following a dose of 100 mg/kg i.p. for 5 consecutive days, with the authors concluding damage to the spermatids.

SUMMARY: The data gap is considered filled as there are studies in the open literature addressing adverse effects in several areas of chromosomal mutagenicity as cited in the above review article.

DNA DAMAGE/REPAIR

50507-001 27258 (New York Med. College, 12/77). Environ. Health Perspectives 21, 79-84. AA, 5/13/85. Ethylene dibromide (purity not indicated) tested in the pol A^+/pol A^- system with E. coli without S9; EDB showed relatively weak positive effect at 10 ul/plate; UNACCEPTABLE (only one dose level, inadequate description of methods, no metabolic activation, no repeat trials, test article inadequately characterized), NOT UPGRADEABLE.

50507-001 11706 (University of Stockholm, 1080). Mutation Research 76, 269-295 (1980). JG, 10/22/86. Review article on EDB and EDC. Cites a study with feeding of ^{14}C-EDB to non-fasted Wistar rats. The radioactivity was incorporated into DNA, RNA and protein of the liver. In addition, they assayed for DNA damage by alkaline elution and found the damage was almost completely repaired by 96 hours. Another report shows EDB given by gavage at 75-100 mg/kg to non-fasted Wistar rats induced DNA synthesis and cell division of hepatocytes with no sign of necrosis at the dosage used. The authors conclude EDB is mitogenic.

While each of the above reports are inadequate, there are sufficient data to assess toxicity. The positive results in several test types indicate EDB is a DNA damaging agent and mutagenic. No further studies are required.

013 934206 EPA Position Document I, 12/77. VdV, 10/17/86. Tox summaries on EDB indicating positive onco effects and also positive mutagenic effects on Salmonella, Neurospora, Drosophila and mouse lymphoma (L5178Y). Adverse effects of EDB in UDS assay with opposum lymphocytes and with mitotic gene conversion in Saccharomyces.

009 934138, 934135, 934144 Summary tables indicating the same adverse